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Visit-to-visit blood pressure variability and longitudinal tau accumulation in older adults

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Abstract

Background: Elevated blood pressure variability (BPV) is predictive of dementia, independent of average blood pressure levels, but neuropathological mechanisms remain unclear. We examined whether BPV in older adults is related to tau accumulation in brain regions vulnerable to Alzheimer's disease, and whether relationships are modified by apolipoprotein $\epsilon 4$ carrier status.

Methods: 286 Alzheimer's Disease Neuroimaging Initiative participants without history of dementia underwent 3–4 blood pressure measurements over 12 months and 1 tau positron emission tomography thereafter. BPV was calculated as variability independent of mean. Each scan determined tau burden (standardized uptake value ratio) for a temporal meta-region of interest, including burden from entorhinal cortex, amygdala, parahippocampus, fusiform, inferior temporal, and middle temporal. Bayesian linear growth modelling examined the role of BPV, apolipoprotein $\epsilon 4$ carrier status, and time on regional tau accumulation after controlling for several variables, including baseline hypertension.

Results: Elevated BPV was related to tau accumulation at follow-up in a temporal meta-region, independent of average blood pressure levels (β : .89 [95% CI .86, .92]), and especially in entorhinal cortex (β : 2.57 [95% 2.15, 2.99]). Apolipoprotein $\epsilon 4$ carriers with elevated BPV had the fastest tau accumulation at follow-up (β : 1.73 [95% CI .47, 3.03]).

Conclusions: BPV is related to tau accumulation in brain regions vulnerable to Alzheimer's disease, independent of average blood pressure. APOE $\epsilon 4$ modified this relationship. Bidirectionality of findings is possible. BPV may represent a marker of vascular dysfunction related to early-stage tau pathology contributing to Alzheimer's disease.

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Keywords

Blood Pressure; Tau Protein; Alzheimer Disease; Aging; Dementia

INTRODUCTION

Blood pressure (BP) and its modulation by antihypertensive treatment has been extensively investigated in relation to cognitive decline and dementia.^{1–7} The role of BP elevation in dementia risk has garnered substantial attention in part because of the clinical availability of BP measures, the high rates of hypertension in older adults, and the wide availability of antihypertensive medications.^{8–10} Recent randomized controlled trial results from the SPRINT study indicate aggressive BP lowering prevents cognitive impairment, relative to standard BP control,¹¹ underscoring the potential importance of BP and its modulation in the prevention of cognitive decline. However, the mechanisms linking BP to cognitive dysfunction have not been fully elucidated.

The role of BP in cerebrovascular disease is well established,^{12–15} but fewer studies have examined whether BP is related to Alzheimer's disease (AD) pathophysiology. Findings to date have suggested that elevated BP may be associated with cerebral spinal fluid (CSF) biomarkers and positron emission tomography (PET) markers of both cerebral amyloidosis and tau-mediated neurodegeneration,^{16–20} as well as AD pathology at autopsy.¹³ More recent studies have particularly emphasized specific links between BP elevation and pathophysiological markers of hyperphosphorylated tau,^{13,16,17,21} as links between BP and amyloid-beta markers have been less consistent.^{15,17} At least one study has suggested tau specific changes may mediate relationships between BP and cognitive impairment, independent of amyloid-beta.²⁰

Beyond average BP and the associated treatment strategies of aggressive BP lowering, other aspects of BP may be important for cognitive decline with potential implications for specific therapeutic approaches. Recent interest in blood pressure variability (BPV) over months to years (e.g., “visit-to-visit” BPV) has emerged as a vascular risk factor for cerebrovascular disease and cognitive decline, independent of average BP levels.^{22–30} Consistent evidence suggests elevated BPV is related both to cerebrovascular disease^{25–27,31,32} and cerebral perfusion decline,³³ particularly within brain regions vulnerable to early-stage AD. However, it remains unclear whether increased BPV may convey risk for dementia purely through its association with cerebrovascular disease, or whether BPV is also linked to AD biomarker abnormality. The only study to examine BPV in relation to AD biomarkers showed no relationship with CSF amyloid-beta or tau levels.²⁰ To our knowledge, no studies have evaluated the relationship between BPV and regional tau accumulation by tau-PET scans. The present study examined the longitudinal relationship between BPV and later tau accumulation in older adults, focusing on temporal regions affected during early-stage AD.^{34,35} The potential modifying role of the apolipoprotein ε (APOE)-4 allele was also investigated. While there is the possibility of a bidirectional relationship between BPV and tauopathy, the present investigation focused on tau changes after BPV was determined.

METHODS

Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The ADNI is a multisite natural history study that has collected clinical, biomarker, and neuropsychological data since 2003 to measure the progression of typical aging, mild cognitive impairment (MCI), and AD. Volunteer adults (age 55–91) were enrolled if they met the following criteria: few depressive symptoms (Geriatric Depression Scale < 6), free of history of neurological disease (other than suspected AD), no greater than mild dementia symptoms (Clinical Dementia Rating scale = 1), and low vascular risk (Hachinski Ischemic Score = 4). Ethical approval was obtained for each institution involved and all participants provided written informed consent. Further study details can be found online (<https://adni.loni.usc.edu>).

The present study included participants who underwent clinical evaluation at study baseline and BP measurement at study screening, baseline, and 6- and 12- months follow-up. Participants also underwent 1 tau-PET scan after the final BP measurement at 12-months follow-up.

Measures

Clinical assessment—Baseline clinical evaluation identified participants to be cognitively normal (CN) or MCI, as described elsewhere,^{33,36} and all participants were confirmed to be without history of dementia or stroke. Briefly, a clinical diagnosis of MCI was given if the following criteria were met:³⁷ subjective memory complaint; Mini Mental State Exam (MMSE) scores between 24 and 30 (inclusive); global Clinical Dementia Rating scale score of 0.5; scores on delayed recall of Story A of the Wechsler Memory Scale Revised Logical Memory II subtest that are below expected performance based on years of education; general presentation that would disqualify for a diagnosis of AD. Participants were categorized as CN if diagnostic criteria for MCI were not met. For the present analysis, CN and MCI participants were combined into one category of older adults without history of dementia or stroke.

BP assessment—Participants underwent seated BP measurement (taken from the dominant forearm arranged at the horizontal level of the fourth intercostal space at the sternum) 3–4 times between study screening and 12-months follow-up using a calibrated mercury sphygmomanometer, as described elsewhere.^{33,36} Intraindividual BPV was calculated for each participant using the 3–4 BP measurements collected over the 12-month period as variation independent of mean (VIM), a commonly used index of visit-to-visit BPV that is uncorrelated with average BP levels across visits^{27,29,30,33,36,38} and was recently shown to predict all-cause mortality better than other indices of BPV.³⁹ VIM was calculated as: $VIM = SD/mean^x$, where the power x was derived from non-linear curve fitting of BP SD against average BP using the nls package in R,⁴⁰ as described elsewhere.^{38,41} Baseline hypertension was determined from the total sample average systolic BP taken at study baseline.

Tau-PET assessment—Participants underwent 1 tau-PET (F-AV-1451 tracer) after the final BP collection at 12-months follow-up. Image acquisition and processing details can be found online <http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/>. Briefly, tau burden (standardized uptake value ratio [SUVR]) was determined from each tau-PET. SUVR values were then intensity-normalized and partial-volume corrected, consistent with other tau-PET imaging studies,³⁴ including those involving ADNI data.⁴² SUVR values were determined for a temporal meta-region of interest (ROI), which has been used in previous cross-sectional⁴³ and longitudinal³⁴ tau-PET studies to separate participants along the AD continuum based on cognitive impairment and abnormal AD biomarkers. The temporal meta-ROI included SUVR values in the entorhinal cortex, amygdala, parahippocampus, fusiform, inferior temporal, and middle temporal ROIs. Finally, ROI and meta-ROI SUVR values were normalized to cerebellum and used in all analyses, consistent with other cross-sectional^{42,43} and longitudinal³⁴ tau-PET studies.

Amyloid-PET assessment—Nearly all (n = 256 / 286) participants also underwent amyloid-PET (Florbetapir tracer). A composite amyloid burden score was calculated and normalized to cerebellum, as described in detail on the ADNI site (<http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/>). An SUVR threshold of 1.11 was used to determine amyloid-PET status; values above this threshold were considered to be “amyloid positive” and values below this threshold were considered to be “amyloid negative” using established criteria (<http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/>).

Other measurements—Baseline clinical evaluation determined several demographic and clinical variables, including: years of education, history of smoking, history of dyslipidemia, global cognition (i.e., MMSE score), use of antihypertensive medication, use of antedementia agents. Participants were categorized at those taking antihypertensive medication (all classes) versus those who were not, and those taking antedementia agents versus those who were not. Vascular risk was also determined from baseline clinical evaluation, as described elsewhere,^{17,36,44} and participants were categorized as having low (< 1 vascular risk factor) or high (≥ 2 vascular risk factors) vascular risk.⁴⁴ APOE ε4 carrier status was determined from baseline venipuncture as previously described⁴⁵ and participants were categorized as those with at least one APOE ε4 allele versus those without.

Data availability statement—All data are available on the ADNI site (<https://adni.loni.usc.edu>).

STATISTICAL ANALYSIS

Bayesian linear growth modeling (brms⁴⁶ package in R⁴⁰ using default prior distributions: fixed effects = improper flat prior over the reals; random effects = non-negative, half Student-*t* prior with 3 degrees of freedom, sigma = 2.5 or median absolute deviation of dependent variable if greater than 2.5) was used to investigate relationships between BPV, APOE ε4, and tau accumulation over time. All models specified random intercepts for participant, to account for individual variation in tau accumulation, and fixed effects for BPV and APOE ε4 carrier status to test for differences in tau accumulation due to BPV and APOE ε4 carrier status, respectively. BPV was handled as a time-invariant variable,

such that a participant's single BPV value determined over study screening to 12-months follow-up was associated with SUVR values at each follow-up tau-PET scan. To help determine the temporal order of any associations, only tau-PET scans acquired after the final BP measurement at 12-months follow-up were used in analyses. Passage of time for tau-PET scans was calculated as months elapsed since BPV determination (range: 12–156 months) and grand centered at 0. Based on emerging evidence that markers of vascular aging may be especially related to tau burden,^{13,17,47} we first ran models investigating a BPV by time interaction on temporal meta-ROI SUVR levels. We then ran models testing the 3-way interaction of BPV by APOE ϵ 4 carrier status by time on temporal meta-ROI tau burden given the established links between APOE ϵ 4, tau, and AD.⁴⁸ For both models, we also explored contributions of individual ROIs included in the temporal meta-ROI (entorhinal cortex, amygdala, parahippocampus, fusiform, inferior temporal, and middle temporal). All models controlled for age at tau-PET, sex, APOE ϵ 4 carrier status (for main effect models), baseline MMSE score, average BP, baseline hypertension, vascular risk, and antihypertensive medication use. Systolic BPV and diastolic BPV were examined separately in all models. The current investigation conducted prespecified analyses with BPV and considered analyses with other more well-studied BP indices (e.g., average BP, pulse pressure, mean arterial pressure) to be beyond the scope of the present study. To test the robustness of primary findings in temporal meta-ROI, sensitivity analyses also covaried for 1) years of education, 2) history of smoking, 3) history of dyslipidemia, 4) use of antimentia agents, and individual contribution of vascular risk factors 5) diabetes mellitus type 2 and 6) atrial fibrillation (versus controlling for overall vascular risk that includes these two factors as defined above). Finally, additional analyses of temporal meta-ROI tau burden were stratified by amyloid-PET status. Non-linear models were attempted but did not result in better fit based on leave-one-out cross validation. All analyses were 2-tailed and effect estimates with credible intervals (CI) excluding 0 were considered significant.

RESULTS

286 participants contributed to 472 tau-PET scans (median 2 scans). The median time interval between BPV measurement and tau-PET scan was 72 months (IQR: 48 months). Table 1 summarizes baseline demographic and clinical information.

Temporal meta-ROI

Increased diastolic BPV was associated with greater tau accumulation in the temporal meta-ROI at follow-up (β : .89 [95% CI .86, .92]) (Figure 1A). Additionally, temporal meta-ROI tau burden increased the fastest for APOE ϵ 4 carriers with elevated diastolic BPV (β : 1.73 [95% CI .47, 3.03]) (Figure 1B).

Systolic BPV was not significantly related to tau accumulation in the temporal meta-ROI (β : .04 [95% CI $-.27$, $.36$]), and this did not differ by APOE ϵ 4 carrier status (β : $-.39$ [95% CI -1.24 , $.44$]).

Individual ROIs

As shown in Table 2 and Figure 2, BPV predicted tau accumulation in all six individual ROIs included in the temporal meta-ROI. Specifically, elevated diastolic BPV was associated with greater tau accumulation in entorhinal cortex (β : 2.57 [95% 2.15, 2.99]), amygdala (β : .66 [95% .56, .76]), parahippocampus (β : .77 [95% .72, .80]), inferior temporal (β : 1.20 [95% .88, 1.52]), fusiform (β : .79 [95% .75, .82]), and middle temporal (β : .72 [95% .70, .75]). Systolic BPV was significantly related to increased tau burden in entorhinal cortex (β : 1.03 [95% .81, 1.25]) and decreased tau burden in middle temporal (β : $-.77$ [95% $-.80$, $-.74$]), but did not significantly predict tau accumulation in other individual ROIs (see Table 2).

Similar patterns emerged at this level for APOE $\epsilon 4$ carriers; regional tau burden at follow-up was related to elevated BPV specifically in APOE $\epsilon 4$ carriers. As summarized in Table 2, APOE $\epsilon 4$ carriers with elevated diastolic BPV were observed to have significantly greater tau accumulation in entorhinal cortex (β : 4.24 [95% 2.15, 6.18]), amygdala (β : 5.07 [95% 4.73, 5.42]), parahippocampus (β : 1.99 [95% .47, 3.55]), and fusiform (β : 1.84 [95% .48, 3.21]), and not significantly greater tau accumulation in inferior temporal (β : $-.39$ [95% -1.23 , .44]) or middle temporal (β : .19 [95% -1.23 , 1.60]). APOE $\epsilon 4$ carriers with elevated systolic BPV had significantly greater tau accumulation in entorhinal cortex (β : 2.13 [95% .45, 3.86]) and middle temporal (β : .54 [95% .42, .68]), but tau accumulation did not significantly differ by APOE $\epsilon 4$ carrier status in other ROIs (see Table 2).

Primary findings remained statistically significant (e.g., CI excluded 0) in sensitivity analyses controlling for years of education, history of smoking, history of dyslipidemia, use of antedementia agents, history of diabetes mellitus type 2, and history of atrial fibrillation (see Supplementary Table S1).

Sensitivity analyses stratified by amyloid-PET status revealed that temporal meta-ROI tau burden increased the fastest for individuals with amyloid-PET positivity and elevated diastolic BPV (β : 4.93 [95% CI 4.62, 5.20]) (Supplementary Figure S1).

DISCUSSION

The present study findings indicate elevated BPV is related to increased tau accumulation over time, specifically within temporal regions known to show tau deposition on tau-PET scans during the early stages of AD. Both systolic and diastolic BPV were examined since prior studies have observed either or both of these to be related to neurocognitive outcomes. Interestingly, diastolic BPV was more consistently related to tau accumulation throughout all temporal regions, but both systolic and diastolic BPV were related to tau within the entorhinal cortex and middle temporal cortex. APOE $\epsilon 4$ carriers with elevated BPV were observed to have the fastest regional tau accumulation, suggesting BPV may be an important vascular risk factor particularly in those at increased genetic risk for AD due to the presence of the APOE $\epsilon 4$ allele. Together these data add to mounting evidence that potentially modifiable hemodynamic factors are related to cerebral tau abnormalities in older adults.^{13,16,17,20,21}

Increased BPV was especially related to tau accumulation in entorhinal cortex, amygdala, and parahippocampus, consistent with other cohort and postmortem studies of tau deposition and spread in AD.^{35,42,49} Classic models of Braak and Braak staging of AD indicate early tau deposition in entorhinal cortex.³⁵ Newer models suggest that other regions may also be vulnerable to tau accumulation earlier in the disease process, which has led to growing investigation of tau burden in meta-ROIs.³⁴ Interestingly, the amygdala is also critical for cortical control of autonomic nervous system activity,⁵⁰ especially sympathetic function,^{51,52} and neurodegeneration in nearby insula has been linked with increases in BPV.⁵³ Regional tau accumulation in the present study was robustly associated with diastolic BPV, which has been hypothesized to reflect endothelial dysfunction and sympathetic nervous system over-activation - compared with systolic BPV reflecting arterial stiffness – although more research is needed.^{30,54,55} Despite the longitudinal design and temporal order of tau-PET scans following BPV measurement, it is not possible to determine causality or directionality of the present findings. Nevertheless, it could be hypothesized that the hemodynamic effects of BPV on the cerebral microvasculature may potentiate tau-mediated neurodegeneration, which has a predilection for autonomic centers such as the amygdala.⁵³ The resulting neurodegenerative effects on autonomic centers could in turn diminish BP regulation and drive further BPV fluctuations.⁵³ This hypothesized scenario of bidirectional causality suggests a potential vicious cycle contributing to AD pathological progression. Future studies should investigate this possibility in order to explore potential treatment implications. Additionally, findings were predominantly observed in individuals with amyloid-PET positivity, consistent with studies suggesting that tauopathy most often occurs in the context of elevated amyloid.⁵⁶

The association between BPV elevation and tau accumulation was particularly apparent in APOE $\epsilon 4$ carriers. There is an increasing appreciation of the vascular contributions of APOE $\epsilon 4$ to cognitive dysfunction in AD. A recent study found APOE $\epsilon 4$ carriers exhibit blood-brain barrier breakdown in the medial temporal lobe,^{57,58} a region where blood-brain barrier permeability⁵⁹ and tau accumulation have been independently linked to cognitive dysfunction.^{34,35} It has been hypothesized that large fluctuations in BP may stretch and distress tight junctions and other intercellular connections^{23,24,60–62} that are necessary to maintain the blood-brain barrier,⁶³ a theory that has found support in rodent calcium chloride models of arterial stiffening.⁶⁴ In APOE $\epsilon 4$ carriers, a blood-brain barrier already prone to “leaking”⁶⁵ may be particularly vulnerable to these hemodynamic forces, which have been coined a “tsunami effect”,⁶² potentially setting the stage for microvascular damage and possibly exacerbating tau vulnerability. Alternatively, tau pathophysiology may exacerbate microvascular damage as seen in tau-overexpressing mice,⁴⁷ adding to the vulnerability of medial temporal regions to vascular insult.⁵⁹ More studies are needed to determine the causal pathways linking BPV to regional tau accumulation in APOE $\epsilon 4$ carriers.

The present findings suggest BPV is related to tau accumulation, a marker of disease progression with growing clinical utility. Importantly, F-AV-1451 tau-PET tracer was recently approved by the FDA for clinical applicability of AD.⁶⁶ BPV may also be a useful marker of disease progression, and one that is both highly modifiable and easily accessible.^{22,54} Some classes of antihypertensive medication may have differential effects

on BPV in risk for stroke, independent of average BP levels.^{67,68} While the current study was not able to address potential class effects on tau accumulation, understanding these differences could inform treatment targets beyond BP lowering.

To our knowledge, this is the first study to examine BPV and tau-PET imaging. One prior study failed to detect any relationship between BPV and CSF tau levels.²⁰ It is unclear why the present study found a different pattern of results, but it could be that CSF tau levels are less sensitive to regional tau deposition within specific brain areas affected in the earliest stages of AD (e.g., the entorhinal cortex) where robust relationships between BPV and tau were observed. This particular study examined day-to-day BPV over an average of 9.1 days,²⁰ suggesting mechanisms underlying BPV may differ by timespan of BP measurement.²² The findings of the present study could suggest vascular dysfunction represented by increased BPV contributes to pathologic tau accumulation; however, replication of the present study finding is needed to further support a role for increased BPV in cerebral tau changes. The longitudinal design and assessment of tau-PET changes after the measurement of BPV represent strengths of the present study. Additionally, BPV was determined from BP measurements obtained using methods standard in routine clinical examination, suggesting BPV is a readily obtained clinic measure. Study limitations include the fact that some aspects of BP collection were not explicitly standardized across sites and may have been collected by individuals who did not have expertise in diagnosing hypertension. BPV was determined from 3–4 BP measurements, consistent with other studies of visit-to-visit BPV in ADNI,^{33,36} but additional BP measurements may improve measurement of BPV.⁶⁹ Antihypertensive treatment initiation, discontinuation, or dosage change over the course of BP measurements were not addressed. The majority of participants in the present study were non-Hispanic White, limiting findings to other racial and ethnic groups. ADNI excludes participants with extensive cerebrovascular burden (Hachinski Ischemic Score \geq 4), precluding investigation of older adults with greater cerebrovascular disease burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX: AUTHOR GROUPS

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PATHOPHYSIOLOGIC NOVELTY AND RELEVANCE

What is New?

- Beyond average blood pressure, high blood pressure variability is linked to dementia risk, although potential mechanisms remain understudied.

What is Relevant?

- Elevated blood pressure variability over one year was associated with tau accumulation in brain regions vulnerable to Alzheimer's disease, especially in individuals at increased genetic risk for Alzheimer's disease.

What are the Pathophysiological Implications?

- Our results support growing evidence linking vascular dysfunction to tau accumulation in older adults at risk for dementia.

PERSPECTIVES

Older adults with greater BPV exhibit increased tau accumulation in temporal regions affected during early-stage AD. The relationship between higher BPV and greater tau accumulation is greatest in APOE ϵ 4 carriers. Findings add to evidence of a link between hemodynamic factors and tau accumulation in older adults at risk for dementia.

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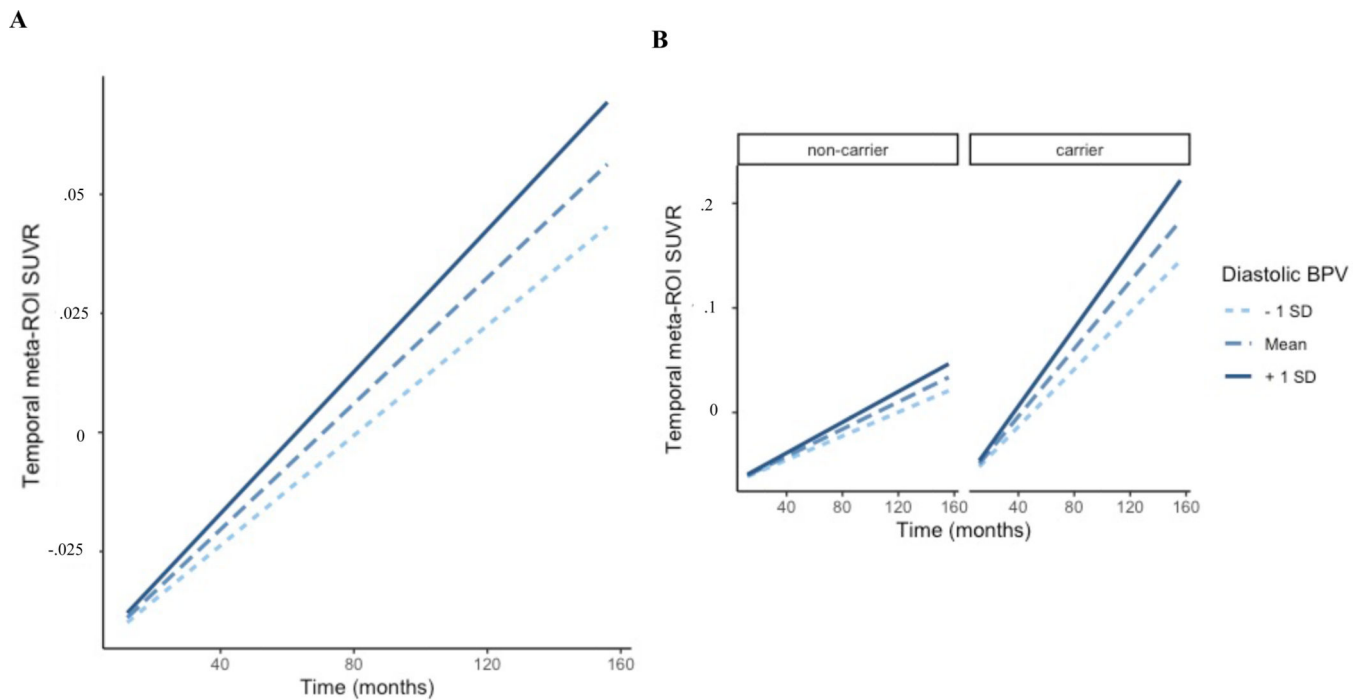


Figure 1. BPV and temporal meta-ROI tau accumulation in older adults

Conditional effects of the interaction of **A**) diastolic BPV by time and **B**) diastolic BPV by APOE ϵ 4 carrier status by time on tau accumulation in temporal meta-ROI in older adults without history of dementia or stroke.

Abbreviations: BPV = blood pressure variability; SUVR = standardized uptake value ratio; ROI = region of interest

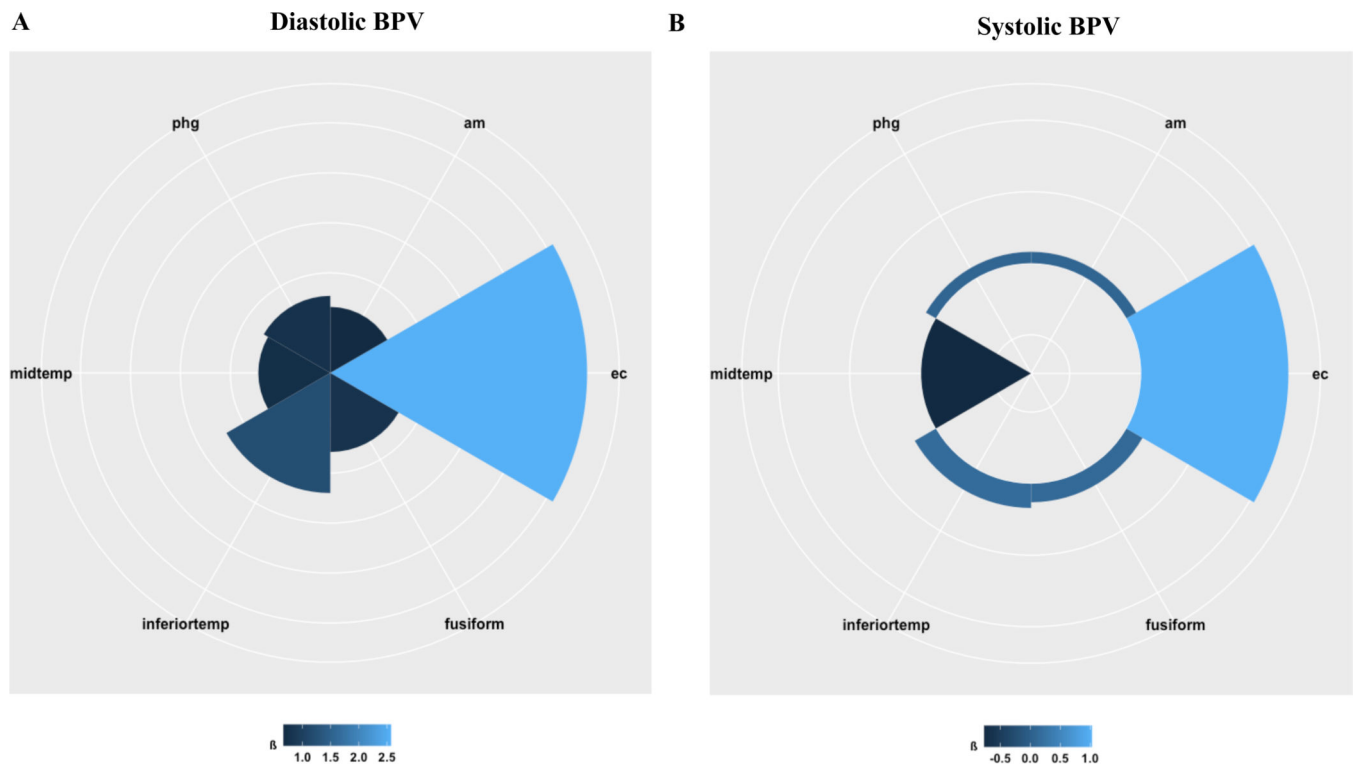


Figure 2. BPV and regional tau accumulation in older adults

Radial plot of the effect estimates (β) of **A**) diastolic BPV and **B**) systolic BPV predicting tau accumulation in individual ROIs included in the temporal meta-ROI.

Abbreviations: BPV = blood pressure variability; phg = parahippocampus; am = amygdala; ec = entorhinal cortex; inferiortemp = inferior temporal; midtemp = middle temporal

Table 1.

Baseline clinical and demographic information.

	Total sample (N = 286)
Age (years)	78.3 (7.3)
Sex (n, % female)	125 (43.7%)
Education (years)	16.4 (2.6)
APOE ϵ 4 carriers (n, %)	100 (35.0%)
ADNI MCI diagnosis (n, %)	130 (45.5%)
MMSE score	28.7 (1.4)
BMI (kg/m ²)	27.7 (5.2)
Vascular risk* (n, % low)	233 (81.5%)
Vascular risk factors (n, %)	
Cardiovascular disease	28 (9.8%)
Diabetes mellitus type 2	22 (7.7%)
Atrial fibrillation	4 (1.4%)
Carotid artery disease	0 (0.0%)
TIA/minor stroke	8 (2.8%)
Medication use (n, %)	
Antihypertensive agents	105 (36.7%)
ACE inhibitors	46 (16.1%)
ARBs	15 (5.3%)
Alpha blockers	10 (3.5%)
Calcium channel blockers	17 (5.9%)
Diuretics	13 (4.6%)
Antidementia agents	14 (4.9%)
Systolic BP (mmHg)	
Baseline	133.9 (15.2)
Average	131.4 (12.5)
VIM	4.9 (3.1)
Diastolic BP (mmHg)	
Baseline	75.7 (9.7)
Average	73.8 (7.8)
VIM	5.9 (1.0)

Means and SDs shown unless otherwise indicated.

* Baseline vascular risk level determined from presence/absence of individual risk factors (history of cardiovascular disease, history of diabetes mellitus type 2, history of atrial fibrillation, history of carotid artery disease, history of TIA/minor stroke). Risk level is low (1 individual vascular risk factor) or high (2 individual vascular risk factors), as described elsewhere.^{17,36,44}

Abbreviations: MMSE = Mini Mental State Exam; BP = blood pressure; BMI = body mass index; VIM = variability independent of mean; APOE ϵ 4 = apolipoprotein ϵ 4; MCI = mild cognitive impairment; CDR-sb = Clinical Dementia Rating Scale sum of box score; A β = amyloid-beta; Ptau = phosphorylated tau; ACE inhibitors = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; ADNI = Alzheimer's Disease Neuroimaging Initiative; TIA = transient ischemic attack

Table 2.

Model estimates of BPV, APOE predicting regional tau accumulation

ROI/meta-ROI	B (95% credible interval)	
	Systolic BPV	Diastolic BPV
Meta-ROI		
Temporal		
BPV x time	.04 (-.27, .36)	.89 (.86, .92)
BPV x time x APOE ϵ 4	-.39 (-1.24, .44)	1.73 (.47, 3.03)
Individual ROI		
Entorhinal cortex		
BPV x time	1.03 (.81, 1.25)	2.57 (2.15, 2.99)
BPV x time x APOE ϵ 4	2.13 (.45, 3.86)	4.24 (2.15, 6.18)
Amygdala		
BPV x time	.08 (-.26, .42)	.66 (.56, .76)
BPV x time x APOE ϵ 4	-.27 (-1.14, .52)	5.07 (4.73, 5.42)
Parahippocampus		
BPV x time	.08 (-.25, .41)	.77 (.72, .80)
BPV x time x APOE ϵ 4	-.38 (-1.22, .45)	1.99 (.47, 3.55)
Inferior temporal		
BPV x time	.17 (-.29, .65)	1.20 (.88, 1.52)
BPV x time x APOE ϵ 4	-.41 (-1.26, .43)	-.39 (-1.23, .44)
Fusiform		
BPV x time	.13 (-.23, .49)	.79 (.75, .82)
BPV x time x APOE ϵ 4	-.38 (-1.21, .45)	1.84 (.48, 3.21)
Middle temporal		
BPV x time	-.77 (-.80, -.74)	.72 (.70, .75)
BPV x time x APOE ϵ 4	.54 (.42, .68)	.19 (-1.23, 1.60)

Models adjusted for age at tau-PET scan, sex, APOE ϵ 4 carrier status, baseline MMSE score, average BP, baseline hypertension, antihypertensive medication use and vascular risk.

Abbreviations: BPV = blood pressure variability; APOE ϵ 4 = apolipoprotein ϵ 4; ROI = region of interest